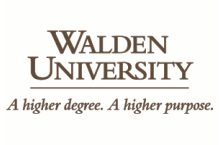

2020

Factors Contributing to Community-Associated Carbapenem Resistant Enterobacteriaceae Infections in the United States

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This is to certify that the doctoral dissertation by

Zabrina Chonita Lockett

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

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2020

Abstract

Factors Contributing to Community-Associated Carbapenem Resistant Enterobacteriaceae Infections in the United States

by

Zabrina Chonita Lockett

MPH, Trident University International, 2009

BS, Trident University International, 2007

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health - Epidemiology

Walden University

February 2020

Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) health care acquired infections are a serious public health threat due to a high mortality rate, economic burden, and depletion of last resort CRE antimicrobials. CRE infections have emerged as community-associated type infections in the United States. For CRE to now have that type of potential is cause for immediate and extensive action. The prevalence of CRE infection cases that were reported as community-associated CRE and health care acquired CRE by examining specific clinical characteristics between 4 selected states that were reported to respective state health departments and the Centers for Disease Control were explored in this study. The theoretical framework most appropriate for this study was the One Health foundation. Two research questions were formulated to address the association of the CRE clinical characteristics (organism identification, specimen source, medical facility type, and laboratory detection method) and the health care acquired Carbapenemase gene mechanism between 4 selected states (Colorado, Illinois, West Virginia, and South Dakota). For this quantitative retrospective study, secondary data was used with the Goodman and Kruskal's lambda analysis. For the 1st time a significant relationship for the clinical characteristics of organism identification and lab gene detection method between the 4 selected U.S. states were established in this study. No relationships were established for the other 3 characteristics but provided insight for future studies. The positive social implication from this study was being able to formulate CRE predictive knowledge that could contribute to the reduction of CRE cases and provide vision to possible reasons why CRE has emerged as community-associated in the United States.

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Dedication

I dedicate this dissertation to my mom (Ruth Ann Lockett), she will always be my hero. The person I am today is because of her strength, her tenacity, and her ability to care for family. My mom worked hard all her life right up to the day she could no longer fight the cancer that invaded all of our lives. I know my mom would be proud of the fact that I fought through all the obstacles and adversities I encountered since her passing to continue to move forward. This doctoral degree belongs to my mom as well as myself. I will always love you momma! You were the best ever! God went above and beyond when you were created…

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

A serious public health threat has been steadily on the rise worldwide since 2000, which is bacterial infections caused by resistance gram-negative bacteria (Kaye & Pogue, 2015). These types of infections are difficult to treat and are categorized as having high morbidity and mortality rates, which are commonly referred to as antimicrobial resistance (AMR) (Chandler et al., 2016; Kaye & Pogue, 2015). As of 2015, AMR cases have been estimated to affect approximately 2 million patients in the United States resulting in approximately 23,000 deaths per year, which is a substantial clinical burden (Kaye & Pogue, 2015). As of 2017, the Centers for Disease Control and Prevention (CDC) estimated that AMR has a substantial economic burden resulting in more than $20 billion per year for health care costs and approximately an additional $35 billion per year to society in lost productivity (van Duin & Doi, 2017).

AMR is a problem domestically and globally, and it has a complex epidemiology that includes multiple levels (Queenan et al., 2016). The U.S. government has issued an official National Action Plan for combating antibiotic resistant bacteria, which means that the United States has enlisted help to provide further guidance to work domestically and globally to prevent, detect, and control antibiotic-resistant bacteria infections that lead to severe illnesses and deaths (The White House, 2015). In this study, I focused on a specific AMR issue, which is Carbapenem-resistant Enterobacteriaceae (CRE) and the community-associated threats in the United States. (Lee et al., 2016). Due to the seriousness of carbapenem antibiotics being considered the last resort treatment for patients with highly resistant gram-negative bacterial infections, community-associated

implications are also a serious threat (Guh et al., 2015). Little research has been done to explore how CRE infections have emerged into being acquired through community-associated transmissions in the United States in addition to the already-established health care acquired transmissions.

Chapter 1 is a summarized overview that includes a brief introduction of AMR, which is followed by background information on CRE about how in the past it has been associated with only health care acquired infections. The problem statement includes evidence with regard to the significance and relevance of how CRE is a threat to the well-being of the public health population in the United States. The overview continues with my purpose in the study, which includes details on the dependent and independent variables for this study. The research questions, hypotheses, and theoretical framework are the main conductors for this research. Chapter 1 also includes information about the nature of this study, conceptual definitions, assumptions, scope and delimitations, and limitations. Chapter 1 concludes information about the significance of the study and a summary, which transitions into the literature review that I present in Chapter 2.

Background

CRE infections have become a serious emerging public health threat (Bartsch et al., 2017; CDC, 2013a; Lee et al., 2016; Tängdén & Giske, 2015). Carbapenems are a class of antibiotics considered to be the last resort antimicrobial agents and are used to treat bacterial infections caused by highly resistant organisms (Lee & Doi, 2014). CRE are considered nonsusceptible to the carbapenem class of antibiotics, which creates limited treatment options for infected patients (CDC, 2015a). CRE infections have one of

the highest mortality/morbidity rates of which some studies have reported a mortality rate to be as high as 40% to 50% for invasive type infections such as bloodstream infections acquired in acute care hospitals and/or long-term care facilities (LTCFs) (CDC, 2015a).

As of 2013, the CDC has documented at least 1 type of infection that has been confirmed as CRE from 42 states within the past 10 years, but from only health care type facilities with other specific characteristic details being sparse (CDC, 2013b). In 2014, the Association for Professional in Infection Control and Epidemiology (APIC) compiled a summary of states that report CRE and have reporting requirements on approximately 19 individual states that voluntarily and routinely define, track, and report CRE cases along with specific collected characteristics to their respective state public health departments (APIC, 2017). It is important to carefully monitor and track the emergence of highly infectious bacterial infections, especially once that infectious state starts to migrate from familiar environments to unfamiliar circumstances. Health organizations that have the abilities to have some type of AMR tracking programs have not always obtained data comprehensively due to practices such as incomplete reporting, practice variance in diagnostics, and undefined or changing definitions for gene resistant phenotype (van Duin & Doi, 2017).

Historically, CRE infections have always been associated with being acquired only within health care facilities in the United States, so with some CRE infection cases now classified as community-associated instead of only health care acquired, this has necessitated a need for an extensive literature review on what could be the causes behind cases of CRE infections acquired through community type exposures (CDC, 2015b;

Saltoglu et al., 2015; Tang et al., 2016). The economic burden of a single CRE infection on average can range from $22,484 to $66,031 for a hospital that contributes to additional length of hospital stay and cost per bed; $10,440 to $31,621 for third party payers that contributes to hospitalizations, drug treatments and additional tests costs; and $37,778 to $83,512 for a public health societal entities that constitutes direct and indirect productivity losses due to mortality costs and years of life lost–patient's life expectancy (Bartsch et al., 2017).

The literature review includes an overview on the background of the historic details of CRE, after which there is a detailed summary and the differences on the epidemiology of health care acquired CRE versus community-associated CRE. Studies on community-associated CRE in the United States were sparse. Global studies on community-associated CRE infections outside the United States were more abundant than community-associated CRE infections inside the United States. In addition, there were also multiple studies done on environmental exposure sources that could also be responsible for community-associated CRE infections. The literature review details are defined in Chapter 2. The independent variable set for this study was 4 geographical state locations. The first dependent variable set for this study was 4 clinical significant CRE characteristics (APIC, 2017). The second dependent variable set was 5 types of confirmed health care acquired Carbapenemase gene mechanisms reported to the CDC from four selected states (CDC, 2017a).

In this study, I examined health care acquired and community-associated CRE clinically significant characteristics from four states Colorado, Illinois, West Virginia,

and South Dakota that report CRE data to their respective public health departments. In addition, I explored the 5 confirmed Carbapenemase gene mechanisms reported to the CDC from the same 4 selected states.

Problem Statement

What has been known in the past is that CRE cases began and have been confined to exist only in health care type facilities (Palmore & Henderson, 2014). Therefore, with recent reports along with certain literature that have supported CRE cases detected in community-associated outpatient type facilities in certain areas, there is confirmation that community-associated CRE infections are no longer nonexistent (Guh et al., 2015; Mortensen et al., 2016; Nordmann, 2014; Santos et al., 2017; Tang et al., 2016). What has not been well documented or specifically characterized is how CRE infections have started to emerge as community-associated in the United States. To explore the migration of CRE from health care type facilities only to also include community type settings it would be productive to examine the clinically significant characteristics from both settings.

The dissemination of CRE infections contained within the health care type facilities have already been established as a serious public health threat, so for CRE to have the potential to spread and/or emerge to cause community-associated infections is cause for immediate and extensive action due to the high fatality rate and economic burden increasing exponentially from CRE (CDC, 2015a). As of 2016, if conditions do not improve to better assess AMR with special attention on CRE at any capacity, it will result in drug-resistant pathogens such as CRE to have the potential to increase

exponentially to 10 million cases with a cost of $100 trillion by the year 2050 (Robinson et al., 2016).

Purpose of the Study

My purpose in this study was to explore the prevalence of CRE infection cases that have been reported between the years 2013 thru 2016 as community-associated CRE cases and as health care acquired cases and compare the similar reported clinically significant CRE characteristics of organism identification, specimen source, medical facility type, and laboratory CRE gene mechanism detection method that have been reported to the respective state health departments in Colorado, Illinois, West Virginia, and South Dakota. I also explored the existence of 5 confirmed Carbapenemase gene mechanisms of Imipenemase (IMP), Verona Integron-encoded Metallo-beta-lactamase (VIM), Klebsiella pneumoniae Carbapenemase (KPC), New Delhi Metallo-beta-lactamase (NDM), and Oxacillinase-48 (OXA-48) from the same 4 states of Colorado, Illinois, West Virginia, and South Dakota complied by the CDC as of 2017 from their Antimicrobial Resistant (AR) Laboratory Network to analyze the association of the confirmed Carbapenemase gene mechanism cases between the 4 states.

Research Questions and Hypotheses

Research Question 1: What is the association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016?

$H_0$1: There is no association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

$H_1$1: There is an association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

Research Question 2: What is the association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

$H_0$2: There is no association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

$H_1$2: There is an association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

Theoretical Foundation

AMR is an issue that encompasses multiple levels of complexity as well as ongoing increased public health threats (CDC, 2013a; Kaye & Pogue, 2015; Sanchez et al., 2013; van Duin & Doi, 2017). CRE is one of the most difficult parts of the whole AMR picture due to very limited to no antimicrobial choices for therapeutic treatment options, so with the recent emergence of CRE cases outside of health care type settings creating community-associated infections a state of alarm has heightened (CDC, 2015a).

The theoretical foundation most suited to tackle such an enormous and complex public health threat such as CRE would best be handled by the implemented concept of One Health (Solomon, 2017).

The theoretical foundation is based on the fact that the health of humans, animals, and the environment intersect each other and should have optimum health through collaborative and cooperation efforts of multiple disciplines working together locally, nationally, and globally to help address the complex public health threat of AMR (Solomon, 2017; USDA/APHIS), n.d.). Because there is a pronounced level of concern for rapidly evolving and highly resistant bacteria such as CRE, the One Health theoretical foundation ideally concentrates on designs, implementations, evaluations, and execution of public health programs that are unique to combating AMR especially CRE (Solomon, 2017), as well as an integrated surveillance framework (Queenan et al., 2016). The One Health concept acknowledges the challenges to combating AMR such as divisions within bureaucratic organizations, non-sharing of important health publication information, and different disciplines not using the same words or definitions to help with comprehension across health care, academic and scientific communities (Solomon, 2017). In Chapter 2, I provide additional detailed information on the history, prior implementations, and a conceptual framework diagram for the One Health theoretical foundation.

Nature of the Study

The nature of this study had a quantitative focus. The quantitative nonexperimental design for this retrospective secondary data analysis study used CRE data previously collected and compiled from four selected state public health departments, which

included Colorado, Illinois, West Virginia, and South Dakota. In addition, secondary CRE confirmed gene mechanisms data from the CDC was also explored.

The independent variable set for this study for both research questions was selected states, which included 4 different geographical locations of Colorado, Illinois, West Virginia, and South Dakota. The first dependent variable set was clinically significant CRE characteristics which included organism ID, specimen source, medical facility type, and laboratory CRE gene mechanism detection methods (APIC, 2017). The second dependent variable set was confirmed health care acquired Carbapenemase gene mechanisms which will included IMP, VIM, KPC, NDM, and OXA-48 reported to the CDC as of 2017 (CDC, 2017a).

Definition of Terms

Carbapenem-resistant Enterobacteriaceae (CRE): Organisms that are nonsusceptible which is considered intermediate or resistant to the antibiotic class of carbapenems (CDC, 2015a).

Carbapenem-producing Enterobacteriaceae (CPE): Organisms that have the ability to pass Carbapenemase, which are mobile genetic elements that transfer to organisms which will make them resistant (CDC, 2015a).

Health care acquired infections: Infections caused by carbapenem resistant organisms patients have acquired within a health care setting also known as nosocomial infections when a hospital stay has been greater than 48 hours within a 2-week period or associated with a long-term care facility (Tang et al., 2016).

Community-associated infections: Infections caused by a Carbapenemase-producing or by carbapenem resistant organisms acquired from a source outside of a health care facility setting (Tang et al., 2016).

Outpatient care facilities: Facilities that administer any type of medical care outside of an in-patient hospital type environment such as but not limited to a doctor's office, urgent care, dialysis center, and/or ambulatory surgical care center (CDPHE, 2017).

Assumptions

I made several assumptions about this study along with the secondary data used. The secondary data collected by each selected state public department of health characteristic categories were not completely similar between each state and some lacked specific details. The CDC collected only confirmed molecular CRE mechanism data from health care facilities. Therefore, even though the secondary data reported was helpful, it lacked cohesiveness to establish a completely accurate representation of exact sources of CRE infection cases in the United States.

Since reading through all of the literature from the literature review for this study antibiotic usage associated with animal and the environment sources could represent an important part to the emergence of community-associated CRE infections, but due to the fact that the state collected CRE data does not represent these specific source areas in the United States, it is not a provable hypothesis for this particular study (Lerner et al., 2013; Robinson et al., 2016) . This study can only bring about awareness to the possibility of alternative sources of CRE exposures from the extensive literature review.

Scope and Delimitations

Due to the seriousness and public health threat CRE possess the scope of this study was limited to analyzing the current existence of CRE cases, both health care acquired and community-associated, and how they have been detected and reported in the United States. Populations excluded from the study were states that did not provide separated detailed information on clinically significant CRE characteristics. This study has limitations on understanding the relationship of how CRE could spread from outside health care facility sources not yet explored in the United States., which is why the literature review focus was broadened to include global, environmental and animal CRE cases that researchers have discovered in other countries. The 4 states selected and data as the focus for Research Question 1 and the CDC gene mechanisms data selected from the same 4 states for Research Question 2 for this study provided a reasonable inference on the generalizability of the results.

Limitation

For a retrospective study using secondary data, my attempt was to determine whether or not the independent variable had an effect on the dependent variables. The fundamental limitation for a study such as this had an apparent weakness due to groups not randomly selected or assigned as well as not being able to manipulate the independent variables. For this study the CRE data reporting to the respective state public health departments is still fairly new and is a work in progress when it deals to the consistency of the specific CRE data details that are reported from each state. The 4 states selected for Research Question 1 were the only states that had a category of community-associated

type CRE cases reported. For Research Question 2, the CDC confirmed CRE gene mechanisms have already been complied into categorized groups. The results for this study were limited to categories versus individual specifics on the community-associated CRE picture. Due to the lack of raw data on community-associate clinically significant CRE characteristics reported and the limited research studies on community-associated CRE studies in the United States. the scope of this study was limited. Even though the scope of this study had limitations it could be the catalyst needed for future studies.

Significance

In this study, I attempted to bring about awareness as to the possibilities of how community-associated CRE infections have emerged and increased in places such as outpatient care facilities in the United States, and the possible modes of transmission of community-associated CRE infections that are different compared to health care acquired CRE infections (Guh et al., 2015; Nordmann, 2014; Tang et al., 2016). To successfully control and reduce CRE infections albeit due to health care-acquired or community-associated sources every entity dealing with health care and/or antibiotics has to be considered for the optimum health for all people, animals and the environment to work together at spreading and sharing valuable CRE information.

In addition, new reporting regulations are needed for understanding the actual incidence rate, the actual prevalence rate, and specific clinical characteristics of all CRE infections to bring about a complete and positive social change for the public's future health against CRE infections and possibly AMR in general. The potential positive social implications consist of improved public health by providing information to help in greatly

reducing the spread of CRE infections as well as a reduction to the overall economic burden of CRE infections, which is associated with the per capita cost of health care. These actions not only help in preserving the carbapenem class of antibiotics for when they are truly needed, but the most important positive social change will be in preserving the quality of life while saving future lives.

Summary

As a health care acquired infection CRE is a serious public health threat component to the AMR picture, so now that there are community-associated cases of CRE that have started to emerge in the United States. the health threat has heightened. There is limited knowledge on how community-associated CRE cases have emerged in the United States. I explored the prevalence of community-associated CRE cases as well as explored the existing confirmed Carbapenemase gene mechanism CRE cases and the threat these types of cases may impose. The knowledge gained from this study could provide future guidance in the reduction of all CRE cases; therefore, resulting in increased positive social change by providing awareness that brings about the reduction of the spread of CRE infections, the reduction in the economic burden of CRE, and preserve the carbapenem class of antibiotics for when they are truly needed preserving the quality of life while saving future lives. In Chapter 2, I provide specific details into the literature review search into the 2 major categories of CRE health care acquired and community-associated acquired as well as specific details on the selected theoretical foundation of One Health for this study. In addition, in Chapter 2, I provide an extensive background and historic details on CRE.

Chapter 2: Literature Review

CRE infections have become a serious emerging public health threat (Bartsch et al., 2017; CDC, 2013a; Lee et al., 2016; Tängdén & Giske, 2015). The history of CRE cases started in and has been confined to only health care type facilities (Palmore & Henderson, 2014). CRE infections have one of the highest case-fatality rates, between 40% to 50% for invasive types of infections such as bloodstream infections (CDC, 2015a). The economic burden of a single CRE infection ranges in the tens of thousands (Bartsch et al., 2017). If there is no cohesive intervention to help decrease CRE as well as other AMR cases the economic burden can exponentially increase to trillions of dollars by the year 2050 (Robinson et al., 2016).

Recent literature have supported CRE cases detected in community outpatient facilities in certain areas, which means community-associated CRE infections are no longer nonexistent (Guh et al., 2015; Mortensen et al., 2016; Nordmann, 2014; Santos et al., 2017; Tang et al., 2016). What has not been well documented and limited knowledge exist is how CRE infections have emerged into the community-associated category in the United States.

My purpose in this study was to explore the prevalence of CRE infection cases that have been reported as community outpatient CRE cases and as health care acquired cases to see if there is an association of the specific CRE characteristics that are reported to the state health departments by states based on different geographical locations. This study also explored the strength of the association of existing confirmed Carbapenemase gene mechanism cases reported by health care facilities.

In addition attention was also needed on community-associated type exposures of CRE to explore other possible risk factors to improve the understanding of how CRE infections have emerged in places such as outpatient care facilities as well as possible modes of transmission of community-associated CRE infections that are different compared to health care acquired CRE infections (Guh et al., 2015; Nordmann, 2014; Tang et al., 2016).

My main focus in Chapter 2 is the extensive literature search conducted for this study. Moreover, I continue with a focus on the history of the theoretical foundation One Health selected for this particular study as well as detailed background information on CRE. Furthermore, an exploration of potential CRE exposure risk factors was also highlighted for this study.

Literature Search Strategy

Chapter 2 encompasses detailed research approaches that I used for the literature review for this study. An extensive review of the literature I conducted included the understanding and clarifications on factors related to CRE incidence, prevalence, explanations, definitions, and theories. The majority of the literature review-concentrated search efforts involved studies on community acquired or associated CRE and CPE in the United States. I selected studies conducted on community acquired CRE and CPE outside the United States, which was a guide to extensively enhance the U.S. community acquired CRE literature search.

Peer-reviewed journal articles and documents I accessed with the assistance of Walden's library databases CINAHL, MEDLINE, ProQuest, PUBMED, and

ScienceDirect in addition to the search engine Google Scholar. Key search terms included the following: *Carbapenem Resistant Enterobacteriaceae or (CRE), Carbapenemase Producing Enterobacteriaceae or (CPE), health care-acquired CRE infections, community-acquired CRE infections community-associated, CRE infections, CRE colonization, United States (U.S.), antibiotic resistance, CRE prevalence, CRE incidence, public health threat infections, One Health, and Antibiotic Resistant Theoretical Framework.* Journal articles and documents were within the date ranges of 2012 to 2018. An abbreviated summary of the search results is listed below in Table 1. In addition to peer-reviewed journals, government and state regulatory and reporting agencies such as the CDC, U.S. Department of Health and Human Services (HHS), I explored The Association for Professionals in Infection Control and Epidemiology (APIC) for guidelines, classifications, and regulations of CRE infections. I selected other recent publications if they were original works and vital and significant supportive literature.

Table 1

Search Results Summary

Database	Search terms	Peer-reviewed selected	Publication date	Results
Medline and CINAHL	*Carbapenem-resistant Enterobacteriaceae* OR *CRE*	No	2012 - 2017	6,840
Medline and CINAHL	*Carbapenem-resistant Enterobacteriaceae* OR *CRE*	Yes	2012 - 2017	2,738
Medline and CINAHL	*Carbapenem-resistant Enterobacteriaceae* OR *CRE* AND *infection(s)* AND *United States* OR *U.S.*	Yes	2012 - 2017	35
Medline and CINAHL	*Carbapenem-resistant Enterobacteriaceae* OR *CRE* AND *colonization* AND *United States* OR *U.S.*	Yes	2012 - 2017	13
Medline and CINAHL	*Carbapenem-resistant Enterobacteriaceae* OR *Carbapenemase-producing Enterobacteriaceae* OR *CRE* OR *CPE* AND *Community-acquired* AND *Infection(s)*	Yes	2012 - 2017	9
ScienceDirect and Google Scholar	*Carbapenem-resistant Enterobacteriaceae* OR *CPE Community-associated CRE infection(s)*	No	2013 - 2017	815
PUBMED	*Community-acquired Carbapenem-resistant Enterobacteriaceae Prevalence*	No	2012 - 2017	78
ScienceDirect and Google Scholar	*Antibiotic-resistant Theoretical Framework* AND *One Health*	Yes	2012 - 2018	40

Theoretical Foundation

The theoretical foundation selected for this study was One Health (OH), which is most appropriate amid the struggle to help reduce antibiotic resistance such as CRE (Solomon, 2017). One Health is viewed as a framework strategy targeted towards reducing risks of infectious diseases by embracing a collaborative approach on health concerns that interconnects human, animal and environment ever constant changes that present those risks (USDA/APHIS), n.d.). The concept that One Health promotes is that people, animals, and the environment can achieve optimum health through continuous joint efforts of all health professionals, scientists, organizations, and disciplines (Solomon, 2017).

The history of One Health dates back to the middle of 1800 by a German scholar who also was a farmer named Rudolf Virchow (USDA/APHIS), n.d.). His philosophy was "Between animal and human medicine there is no dividing line – nor should there be. The object is different but the experience obtained constitutes the basis of all medicine" (USDA/APHIS, n.d., p.1). Nearly, 75 percent of emerging infectious diseases within the last 30 years among humans has had a connection to a zoonotic type diseases transmitted between animals to human (USDA/APHIS), n.d.). Examples of such animal to human zoonotic transmitted diseases are below listed in Table 2 (USDA/APHIS), n.d.).

Table 2

Animal to Human Zoonotic Diseases

Infectious diseases	Infectious agents	Source	Year
Human tuberculosis (TB) 20% cases	*Mycobacterium bovis*	Cattle	Mid-1900s
Human Brucellosis – 29,600 cases	*Mycobacterium bovis*	Cattle	1930-1941
H5N1 virus	Pathogenic avian Influenza A	Birds	2006
Swine flu	Pathogenic type A Influenza	Pigs	2012

By 1980 Calvin Schwabe modernized the One Health theory by advocating for a human and veterinary unification approach to combat zoonotic diseases (USDA/APHIS), n.d.). By 2007, the American Medical Association (AMA) and the American Veterinary Medical Association (AVMA) put together an One Health Initiative (OHI) task force which included a host of world agencies such as but not limited to the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the world Organization for Animal Health (OIE) just name few collaborations (USDA/APHIS), n.d.).

The Institute of Medicine (IOM) and the National Research Council (NRC) have advocated that human health is linked to animal health and the ecosystem health (Rubin et al., 2013). For the last 2 decades both the IOM and NRC have promoted publications and workshops addressing the shift to the implementation of One Health in order to

capture the potential threats that involve the connect of human, animal, and ecosystem risks (Rubin et al., 2013).

One Health is the most appropriate framework essential for undertaking antibiotic resistance issues. Antibiotics that are used for humans and animals share some of the same molecules which makes transmission of resistance easier than realized between humans and animals directly or by way of the environment (Robinson et al., 2016). If collaborative efforts are not put forth by all respective public health entities to help tackle AMR such as CRE then drug-resistant pathogens have the potential to reach over 10 million by the year 2050, which could cost the U.S. almost $100 trillion between now and 2050 from food globalization, livestock movement, agriculture production, human travel, and AMR gene transfer (Robinson et al., 2016).

A conceptual illustration of One Health surveillance framework is depicted below in figure 1 (Queenan et al., 2016). This framework expands the surveillance from just solely focused on human antibiotic usage and consumption data from hospitals and community to also the incorporation of the surveillance data sharing, usage, and consumption from animals, food and the environment (Queenan et al., 2016).

Figure 1.

One Health Conceptual Framework

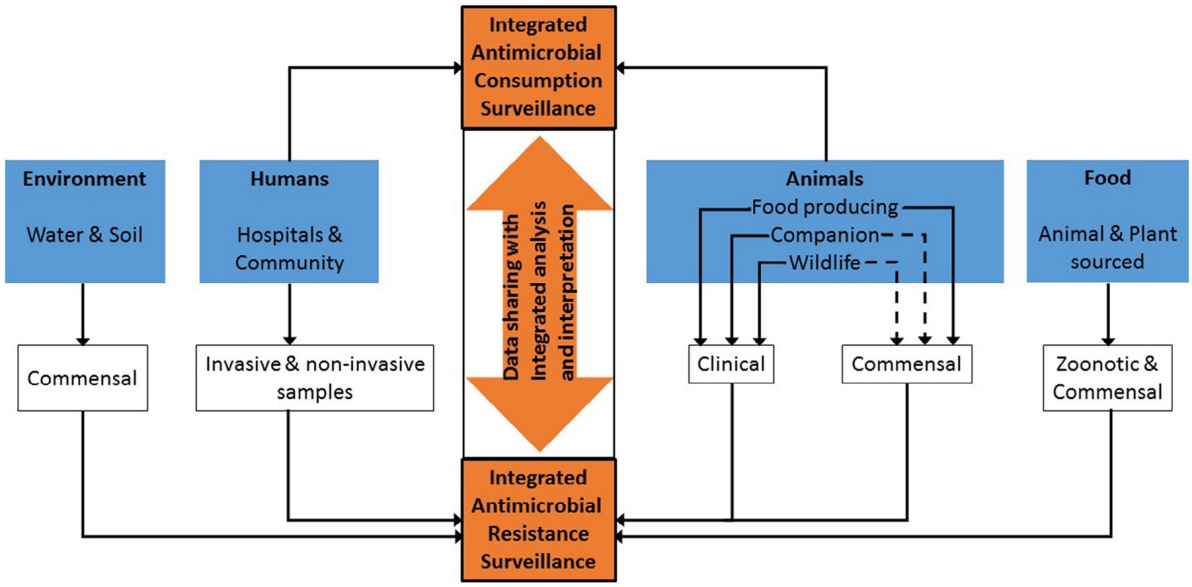

Figure 1 depicts One Health surveillance framework that visually integrates the AMR and antimicrobial consumption for environment, humans, animals, and food.

One Health is vital to the increasing profound crisis of AMR especially like CRE and to understand and apply the One Health approach to public health policies and programs which can help bring together different expertise across a broad field to include human, animal, and environment health will be extremely useful (Solomon, 2017). The implementation of One Health for some organizations, scientific entities, public health leaders and health care professionals have encountered some challenges and barriers such as varied jargon, bureaucratic divisions, and academic/scientific differences, but these challenges are easier to overcome than the increasing CRE situation in the United States. from unknown community sources (Solomon, 2017).

In this study I depict the urgency and importance of the implementation of One Health by exploring possible community-associated sources that can put the public's health at risk for AMR such as CRE. The research questions help to show there is a lack of collaboration between entities that currently exist in order to determine how community-associated CRE is now a possibility in the United States. as well as help build upon existing theories of community-associated CRE.

CRE Epidemiology

Carbapenems are a class of beta-lactam antibiotics that includes meropenem, imipenem, ertapenem, and doripenem and are now considered a last resort treatment agent for highly resistant gram negative organisms in the Enterobacteriaceae family (Lee & Doi, 2014). Previously, carbapenems were considered highly effective broad-spectrum antimicrobials. Imipenem and meropenem were introduced in the 1980s, ertapenem was introduced in 2001, and doripenem is considered the latest member to be added to the carbapenem class (Perez & van Duin, 2013). The prevalence of CRE infections were extremely rare more than a decade ago and since their first appearance CRE infections have rapidly spread at an alarming rate (Rolain & Cornaglia, 2014).

The first organism identified to exhibit a resistance characteristic to a carbapenem was *Klebsiella pneumoniae* and it was resistant to imipenem back in 2004 (Guh et al., 2014). This resistance classification was named *Klebsiella pneumoniae* Carbapenemase (KPC) and some patients acquired KPC infections rapidly and steadily increased through to 2010. By 2006 Carbapenemase-producing organisms started to emerge due to the drastic increased use of carbapenems, which contributed to the classification of CRE

(Guh et al., 2014). The antibiotic resistance gene/plasmid mechanism that creates CRE is an element that is genetically mobile and has escalated the multidrug resistant bacteria categories (Kaye & Pogue, 2015). Due to the mobility quality of resistant gene mechanism new antibiotic resistance bacteria can emerge at any time from person to person and/or from nonhuman sources in the environment (Kaye & Pogue, 2015).

Antibiotic resistance is the product of frequent widespread use of antibiotics appropriately and inappropriately without the proper dissemination of mobile resistant gene mechanisms, which is widely misunderstood by many health care and community care professionals (Guh et al., 2014). Since this factor has emerged it marked the end of just KPC existing and the beginning of the entire family of Enterobacteriaceae, which consists of all the gram negative bacteria being susceptible to inheriting a Carbapenemase resistant gene mechanism (Guh et al., 2014; Rolain & Cornaglia, 2014).

The main mechanism that produces Carbapenemase to exist in certain organisms is known as β-Lactamase hydrolysis, which is broken down into Ambler classifications, of which are displayed in Table 3 the β-Lactamase Ambler classifications (Kaye & Pogue, 2015).

Table 3

β-Lactamase Ambler Class Summary

Ambler class	β-Lactamases	Enzyme example	Typical organism producing the enzyme
A	Penicillinases	KPC – *Klebsiella pneumoniae* Carbapenemase	*Klebsiella* species, *Escherichia coli,* *Enterobacter* species
B	Metallo-β-Lactamases	NDM – New Delhi Metallo-β-lactamase IMP – Imipenemase VIM – Verona Integron-encoded Metallo-β-lactamase	*Klebsiella pneumoniae, K. oxytoca, Escherichia coli,* *Enterobacter* species
C	Cephalosporinases	AmpC	*Enterobacter* species*,* *Citrobacter* species, *Pseudomonas aeruginosa*
D	Oxacillinases	OXA	*K. pneumoniae, E. coli,* *Acinetobacter baumannii*

KPC, NDM, IMP, VIM, AmpC, and OXA are examples of the designated resistant gene mechanisms; patients with bacterial infections caused by these Carbapenemase producers will be at a higher risk of morbidity and/or mortality. Identification of CRE gene mechanisms is an important step to the identification of which patients are infected with what mechanism in order to properly apply surveillance to keep transmission of gene transfer low (Kaye & Pogue, 2015; Rolain & Cornaglia, 2014).

There was a study conducted on antimicrobial resistant *Klebsiella pneumoniae* from surveillance data that totaled 3,132,354 cases collected from 1998 thru 2010 from a surveillance network and the results confirmed a significant increase of resistant to multiple antimicrobials (Sanchez et al., 2013). Starting at the end of the 20th century to the beginning of the 21st century AMR has grown into a significant health risk domestically especially when it involves gram-negative bacteria due to the increased resistance mechanisms, the spread of resistant strains from person to person, and/or from environmental sources. The threat of CRE infections and the imposed burden is increasing for the public health population in the United States (Kaye & Pogue, 2015; Sanchez et al., 2013).

The CDC assigns different warning levels of threat specific hazards for infectious agents that have become a major concern and is highly suggested to be monitored and tracked (CDC, 2013a). There are 3 different warning level hazard categories starting with the lowest level of *Concerning*, the next level is *Serious,* and the highest level is *Urgent*. CRE has been assigned the *Urgent* warning hazard level due to having the status of very limited therapeutic options for treatment or completely untreatable infections involving patients within health care facilities (CDC, 2013a). The *Urgent* level warning is the highest consequence antibiotic-resistant threat and can have the potential ability to become widespread. As of 2013 in the United States. there has been an average of 9,000 CRE infections with 600 deaths per year (CDC, 2013a). The concern that exist is that the CDC is only collecting and reporting on health care-acquired CRE confirmed specific

carbapenem mechanism cases and not CRE cases that are starting to emerge as community-associated cases (CDC, 2017a).

Health care Acquired CRE Epidemiology

A basic definition for health care acquired CRE are infections caused by carbapenem resistant organisms that patients have acquired only within a health care facility type setting (also known as nosocomial infections) when a hospital stay has been greater than 48 hours within a 2-week period or associated with a long-term care facility. CRE infections commonly poses a threat to patients exposed to high-risk infectious environments in a health care type setting (Tang et al., 2016). CRE generally exists in a patient as an infection, which causes a host of associated symptoms and/or disease to any part of the infected body site (CDC, 2015b). In addition, a patient can also be colonized with CRE, which means CRE exists in the body but is not causing symptoms or disease. CRE transmission to other patients and/or medical equipment presents the same risk to other patients whether CRE is classified as an infection or colonization (CDC, 2015b). An incidence rate of 2.93 per 100,000 population for CRE in the United States. would equate to about 9,418 infections, which is a sizeable economic burden of about $275 million for hospitals if the severities of CRE infections are not fully comprehended and many health care professionals continue to be naïve to the ill effects of CRE infections (Bartsch et al., 2017).

CRE infections have started to emerge in patients linked to community-associated type setting exposures without ever having been associated with a health care facility. A recent study supports that health care facilities' infection control and prevention methods

have been inadequate in the spread and/or control of CRE (Thaden et al., 2014). The study results revealed that CRE infections went from (0.26 cases per 100,000 patient-days) in 2008 to (1.4 cases per 100,000 patient-days) in 2012, which is almost a 5-fold increase (Thaden et al., 2014). CRE has varied in the scenarios and setting of spreading patterns, which could explain the migration to community-associated exposures. Community type exposures will definitely not have the specific control measures, regional support, or facility level infection control. Any facility administering medical care should employ an effective CRE prevention, control, and tracking strategies, which means all entities will have to work together because even health care facilities are finding CRE infections challenging to prevent, control, and track (Lee et al., 2016).

Community-Associated CRE Epidemiology

The basic definition for community-associated CRE is any infection caused by a Carbapenemase-producing or by carbapenem resistant organisms that patients have acquired outside of a health care facility type settings (Tang et al., 2016). Very few studies have been done to explore how CRE infections have started to emerge through community-associated transmission in the United States. One study conducted a comparison on urinary tract infections from community-onset health care type facilities and hospital type facilities and established that community-onset health care associated (CO-HCA) infections are a newly defined category for multi-drug resistant organism infections (Saltoglu et al., 2015). Not only are the characteristics of acquiring CRE changing, but the CRE transmission status is also changing from strictly nosocomial bacterial infections to also included community-associated bacterial infections

(Nordmann, 2014). Through the literature reviewed community-associated CRE cases started to take form by focusing on specific clinically significant CRE characteristics of the organism identified, the specimen source, the Carbapenemase gene mechanism detection method identified, and the medical facility type in which the patient was associated when identified to have CRE infectious (Guh et al., 2015; Kaye & Pogue, 2015; Rolain & Cornaglia, 2014; Tang et al., 2016). One of the most valuable studies done was in Taiwan set the precedence for this study and that study looked at and determined that it was important to examine the clinically significance characteristics of pathogens, clinical sources, facility types, antibiotic resistance patterns, and demographics to determine that CRE infections originating from both health care acquired and community acquired facilities (Tang et al., 2016). The literature reviewed for community associated CRE has been categorized into 3 different sections: (1) domestic represents the few studies conducted in the United States.; (2) globally represents the broader studies conducted in countries other than the U.S.; and (3) environment represents a new transmission risk category for CRE.

Domestic

Community-associated CRE is on the rise in the United States. and not many studies exist that have explored the reasons as to how a strictly health care acquired infectious condition is now emerging into and can be acquired through community-associated transmissions.

When Methicillin-Resistant *Staphylococcus aureus* (MRSA) was first reported back in 1961 it to was acquired in only health care type facilities and it took some time to

determine that the resistance was the production of a horizontal gene transfer of the *mecA* gene (Stryjewski & Corey, 2014). By the early 1980's *Staphylococcus aureus* had morphed into being resistant to multiple antimicrobials and was considered an epidemic until major efforts were implemented to truly track and prevent the spread of health care-acquired MRSA (Stryjewski & Corey, 2014). By the 1990's a new epidemic had emerged and was determined to be community-acquired MRSA, which was later confirmed to be transmitted from person to person through purulent skin infections amongst young people with no exposure to any health care facility (Stryjewski & Corey, 2014). Now the same scenario is happening with CRE infections, but under different circumstances. Until the transmission factors are completely understood for the emergence of community-associated CRE infections the public's health is at risk.

One of the few studies conducted looking at community acquired CRE was a seven U.S. metropolitan areas study that suggested the CRE cases determined to be community acquired may have been from CRE cases that existed earlier when patients were hospitalized with prior infections from sterile sites and urine specimen sources and then later discharged to other medical care type facilities. The study further suggested that local efforts may need to be employed in order to help with the prevention and spread of CRE transmission (Guh et al., 2015).

Thaden et al. (2014) provided evidence that 25 southeastern community hospitals in the United States. detected numerous CRE isolates from asymptomatic colonized patients and prospectively entered the CRE information into a centralized database from 2008 to 2012, not only did this help keep track of the number of CRE cases but it also

helped determine the clinical characteristics of these specific CRE cases in order to help the 25 community hospitals respond to CRE in a proactive manner through dissemination of information (Thaden et al., 2014).

After a CRE characterization study was conducted in a tri-state region in the United States. consisting of Ohio, Kentucky, & Indiana it recognized that although CRE has been primarily associated with transmission through health care type settings, community-acquired transmissions do exist and it will be important for future endeavors to understand this type of movement of resistance in order to respond to local and regional trends (Mortensen et al., 2016). Although few studies have been conducted on community-associated in the United States. the studies have offered some entry-level information on community-associated CRE, but overall knowledge remains limited and community-associated CRE is still not well defined or encompassing.

Globally

There have been many more studies conducted on community-associated CRE outside the U.S. Considering the sparse amount of literature for community-associated CRE in the United States. information regarding community-associated CRE globally was also reviewed in order to get a more in-depth prospective on risks, prevalence, incidence, and characteristics of CRE transmission through community associations. One study on community-associated CRE infections in Taiwan, suggested that the clinical characteristics were different for community-associated CRE from health care acquired CRE infections clinical characteristics; therefore, further larger studies are needed to study more clinical significance differences especially in the United States. (Tang et al.,

2016). The most common characteristics for community acquired CRE cases discovered during the study conducted involved elderly females with UTIs whereas the health care acquired CRE cases involved more intra-abdominal infections and indwelling device infections (Tang et al., 2016).

Zimmerman et al. (2013) researchers provided compelling evidence from an investigative study conducted in Israel that suggested an initial diagnosis of a positive CRE culture could have a mean time of 387 days to proven CRE negative. One hundred thirty-seven hospitalized patient records with positive CRE cultures from 2009 to 2010 were subjects selected for the study. Twenty-one of the 137 patients were initially diagnosed CRE positive as an outpatient, so not all of the positive CRE cases originated in the hospital. Many factors that revealed the mean time of 387 days of CRE carriage included repeat hospitalizations, seriousness of the cofounding illnesses, staff exposure time to the infected patients, and the lack of monitoring antimicrobial usage of patients discharged (Zimmerman et al., 2013). The carriage time of more than a year from CRE positive to CRE negative could have significant influence on the exponential rise and spread of CRE to the community setting. In addition, another recent prospective observational study illustrated an alarming high prevalence of community associated multi-drug resistant organisms (MDRO) colonized in East India patients and highlighted the fact that the prevention of antibiotic misuse in the community can help minimize this critical problem (Thacker et al., 2014).

A more recent study reported that an outpatient admitted to a Portuguese hospital had a community associated CRE infection, which was acquired through possibly

horizontal gene transfer (Santos et al., 2017). Horizontal gene transfer involves CRE strains that have moved between inpatients and outpatients through human gut colonization and carried beyond the hospital environment. This was evidence that improved containment measures for antibiotic resistant stewardship are needed for both inside and outside medical facilities due to evidence of inter-institutional gene transfer from hospital to dissemination into the community (Santos et al., 2017).

A study conducted in 3 Lebanon medical facilities tried to determine if there were comparative data differences between community-acquired infections (CAI) and health care associated infections (HAI) (Dabar et al., 2015). The characteristics examined were population characteristics such as age comorbidities like diabetes, cirrhosis, & cancer; and heterogeneity characteristics such as microbial infection organism, site of the infection, and microbial resistance gene pattern (Dabar et al., 2015). The type of infections determined if there were significant differences between the 2 groups CAI and HAI concluded in the following results. Respiratory tract infections represented the most common infection for both groups, but very small significance in characteristic differences between the 2 groups (Dabar et al., 2015). Urinary tract infections (UTIs) represented a fairly good number in the HAI group with an even higher number for the CAI group; moreover, the study concluded that UTIs could be the explanation of factors causing resistant bacteria to emerge and increase within the community due to the usage of antibiotics not being monitored properly and not tracking if the patient CRE UTI infection actually resulted as negative (Dabar et al., 2015).

A retrospective matched case-control parallel study conducted in a hospital in Central South China where carbapenem resistant *Escherichia coli* (CREC) specifically targeted to examine the risk factors and scarcity of data to the increased emergence and spread of CREC in health care associated facilities, which has become a serious problem in Chinese hospitals (Meng et al., 2017). The multivariate conditional logistic regression analysis helped conclude several risk factors such as prior hospital stays are highly associated with health care acquired CREC; carbapenem exposure and urinary tract disease along with additional comorbidities such as anemia and/or high blood pressure were regarded as important co-risk factors as well. It was theorized that the environment encompasses a reservoir that is limitless when it comes to AMR genes and more patients are carriers of antibiotic resistant organisms (Meng et al., 2017). It was determined and highly suggested that implementation of infection control processes and antibiotic stewardship across all health care type entities could greatly help with the reduction of the emergence and spread of CREC (Meng et al., 2017).

A prospective observational study done involving two Korean community hospitals supports the theory that highly extra-intestinal pathogenic *Escherichia coli* (ExPEC) which is an extended-spectrum-β-lactamase producer isolated from many UTIs in health care facilities was the resistant suspect gene that caused the drug resistant organism to migrate to community facilities. This study highly suggests that UTIs are a major concern for community onset bacterial resistant infections and should not be ignored especially for the asymptomatic carriage individuals who are healthy without prior exposure to antibiotics (Kim et al., 2017).

Tängdén & Giske (2015) expressed concerns that the possibility of untreatable community acquired urinary tract and bacteremia infections caused by carbapenem resistant E. coli are on the rise, which is a major public health threat. All medical professionals and all medical facilities should be aware of this threat as well as be aware of how to appropriately treat and manage patients with true CRE infection and those patients that are just colonized due to the rapid global dissemination of Carbapenemase (Tängdén & Giske, 2015).

Lastly, a comprehensive analysis was conducted on Carbapenemase producing Enterobacteriaceae (CPE), non-nosocomial infection, epidemiological characteristic features in Spain (Palacios-Baena et al., 2016). The breakdown of reservoirs for CPE non-nosocomial infections were colonized patients from nursing homes and acute care hospitals contributing to the frequent lower urinary tract infections into the community (Palacios-Baena et al., 2016).

Overall the global studies reviewed helped established and highlighted that there are many opportunities for CRE to spread whether initially acquired in a health care type setting or not will eventually find a way out into the community setting albeit from prior CRE infections not completely treated, improper use of antibiotics, no communication of current or past patient medical history of CRE infections.

Environmental

Upon review of the literature it was revealed in global studies that a possible transmission mode for CRE could be factors related to the environment. After this knowledge was uncovered in the literature it was also explored as to how the

environment would be a mode of transportation for CRE exposure risk. Multiple studies were reviewed below to highlight just what some of those environmental factors could include.

Palmore & Henderson (2013) researchers addressed the fact that asymptomatic carriers can easily transmit resistant gram-negative pathogens to the environment in varying degrees. Identifying colonized patients is extremely important for the reduction of spreading factor of infections (Palmore & Henderson, 2013). If colonized asymptomatic carriers of CRE are an unrelenting challenge for health care facilities, then having those same carriers out in community-associated type settings will make it extremely difficult for detection and surveillance measures for CRE infections. This study also theorized that sink drains and ventilators used in the presences of infected patients could possibly be a source of transmission of resistant pathogens if not properly decontaminated (Palmore & Henderson, 2013).

Abraham, Wong, Turnidge, Johnson, and Trott (2014) researchers hypothesized that the close relationship between humans and their pets could contribute to the expansion of Carbapenemase-producing bacteria by way of cross-species transmission, which would be considered an unnoticed source for multi-drug resistant gram-negative bacteria to become community associated. Organisms such as *Escherichia coli* that carry the NDM-1 and/or the OXA-48 genes and OXA-48 *Klebsiella pneumoniae* have been isolated from companion animals with clinical infections. Laboratories that deal only with veterinary diagnostic medicine will not have the necessary knowledge to diagnosis or provide treatment for animals that have CRE infections due to the fact that carbapenems are not a

registered antimicrobial for animals in the United States. It has been documented that on rare occasions a veterinarian has used carbapenems as an off-label treatment for dogs with multi-drug resistant UTIs (Abraham et al., 2014).

Guerra, Fischer, and Helmuth (2014) researchers presented a study that proposed the presence of gram-negative organisms that carry the Carbapenemase genes involving food producing sources like livestock; wildlife and seafood in the environment have been exhibited, which makes sense because of the relationship of gram-negative organisms and soil along with irrigation water sources. The actual prevalence of zoonotic bacteria that carry Carbapenemase genes are not known, which is a problem because food sources along with other animal sources are a huge concern. With recent knowledge of food sources at risk for environmental CRE exposures there has not been as of yet any official reported retail meat or other food items possibly contaminated with CRE organisms through environmental exposures only observational reports, which makes the situation a reality (Guerra et al., 2014).

Carbapenemase-producing *Salmonella species* were isolated from pig sources at a swine farm in Germany. *Salmonella species* with the Carbapenemase-producing gene were isolated from beef and buffalo sources in India and CRE E. coli was isolated from oysters and shrimps from pond water sources in Brazil. The authors also proposed the existence of CRE in companion animals of which Carbapenemase-producing OXA-23 *Acinetobacter species* was isolated from 20 horses that required hospitalization in Belgium and NDM-1 producing *Escherichia coli* was isolated from canines and felines recently in the United States. The authors theorized that the abusive behavior of

antimicrobial medicine usage by humans and possibly the present of hospital waste is the link to the environment presence of CRE (Guerra et al., 2014).

Antibiotic resistance and food safety have already become a reality and challenge in the United States. Due to improper use of antibiotics in humans and what is termed as food animals (CDC, 2017b). A foodborne illness is normally a self-limiting condition, but if the illness is a severe case that requires antibiotics the ability to treat if the bacteria is antibiotic resistant will be a challenge. A limited treatment option for the patient not only puts that patient at a high mortality risk, but the public health threat has increased (CDC, 2017b).

Summary

In summary, health care acquired CRE in the United States has already been established as a public health threat, an enormous economic burden, and has extremely high mortality rates (Bartsch et al., 2017; CDC, 2013a; Lee et al., 2016; Tängdén & Giske, 2015). CRE has started to emerge outside of health care type facilities and into community type settings in the United States. And little research has been done to explore how CRE infections have emerged into being community-associated type transmissions in the United States. Literature was reviewed from multiple global sources to explore possible factors as to how CRE transmission can migrate from health care-acquired to community-associated and what possible clinical significant CRE characteristics are common and/or different than health care acquired CRE transmissions (Guh et al., 2015; Mortensen et al., 2016; Nordmann, 2014; Santos et al., 2017; Tang et al., 2016).

My purpose for this study was to examine the prevalence of what already exists in the United States on community-associated CRE infections as well as health care-acquired CRE infections and compare the differences of the CRE characteristics. The theoretical framework selected for this study was One Health, which embodies that optimum health be established for people, animals, and the environment (Solomon, 2017). No one entity has the capability to successfully improve population health alone especially when dealing with CRE, which is why a collaborative effort is needed across multiple health care and community, care medical systems.

A brief history on CRE epidemiology was provided to better understand the origin of carbapenems and on how CRE came to exist (Guh et al., 2014; Rolain & Cornaglia, 2014). Epidemiology factors were provided on health care acquired CRE and community-associated CRE. Community-associated CRE reviewed literature was further broken down into 3 different categories domestic, global, and environmental. The community-associated CRE literature domestically embodied the U.S., but only a few studies were conducted. This study has added to the small list of existing studies conducted in the United States. while also providing a catalyst for other similar future studies. Although out of scope for this study literature review on environmental sources of CRE transmission was quite compelling and introduced factors that exist but have not been explored in the United States. before, which presents another facet on the emergence of CRE in the United States. Chapter 3 provides details on the population selected, the methodology, and data analysis plan that was used to determine whether or not an association exists between clinically significant CRE characteristics and whether

or not an association exist between confirmed health care acquired Carbapenemase gene mechanism between 4 selected states.

Chapter 3: Research Methodology

Introduction

My purpose in this study was to explore the prevalence of CRE infection cases that have been reported during 2013 to 2016 as community-associated CRE cases and as health care acquired CRE cases that have similar clinically significant CRE characteristics reported to the selected 4 respective state health departments to determine whether there was an association. In this study, I also explored the existence of 5 different confirmed Carbapenemase gene mechanisms compiled by the CDC between 2016 and 2017 from the selected 4 states to determine whether there is an association between those particular 5 confirmed Carbapenemase gene mechanisms and the 4 selected states.

Chapter 3 is an overview of the research design and rationale for the study. In this chapter, I cover details on the sample selected, the population targeted, the sampling procedures, and the data collection. I state the dependent and independent variables along with selected data analyses plan. The end of the chapter entails a discussion of the possible threats to the internal and external validity along with the ethical procedures finally followed by a summary.

Research Design and Rationale

The research design that I selected was a retrospective causal-comparative design I to explore an occurrence that already exists. This quantitative nonexperimental retrospective process was the most appropriate design selection for this study to look back at secondary data to see whether the dependent variables were affected by the independent variables.

The selected research design assists with the exploration of the prevalence of community-associated and health care acquired CRE cases with similar clinically significant characteristics by using nonprobability sampling secondary data from the public health departments from 4 selected states and confirmed Carbapenemase gene mechanisms from the same 4 selected states and compiled by the CDC from the AR lab network. There was 1 independent variable, group of states, in the United States, for both research questions which included Colorado, Illinois, West Virginia, and South Dakota. There were 2 different dependent variable sets for this study. The first dependent variable set for this study was 4 clinically significant CRE characteristics, which included organism ID, specimen source, medical facility type, and laboratory gene mechanism detection methods (APIC, 2017). The second dependent variable set was confirmed health care acquired Carbapenemase gene mechanisms, which included 5 groups IMP, VIM, KPC, NDM, and OXA-48 reported to the CDC as of 2017 (CDC, 2017a). The variables groups for the study cannot be manipulated, which presented some design weaknesses by not being able to randomly select specific groups, but is a way to link present events to past events (Creswell, 2009). Studies on community-associated CRE are sparse in the United States and this design choice helped to bring about awareness and helped advance the knowledge of the origin of community-associated CRE infections by providing valuable information on the association that exists between the 4 states that reported community-associated and health care acquired CRE infections from 2013 to 2017 for future studies to build upon.

Research Questions and Hypotheses

Research Question 1: What is the association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographic location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016?

$H_0$1: There is no association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection methods and geographic location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

$H_1$1: There is an association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection methods and geographic location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

Research Question 2: What is the association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographic location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

$H_0$2: There is no association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographic location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

$H_1$2: There is an association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographic location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

Methodology

Setting and Sample

Data that I used for this study to address the first research question were from departments of health from 4 selected individual states that implemented require statewide reporting of CRE information. Although each state had different CRE informational reporting requirements a summary list of which states reported CRE information to their respective departments of health was compiled in a summary report by the (APIC, 2017). The states selected for this study with reported CRE epidemiology information included Colorado, Illinois, West Virginia, and South Dakota (CDPHE-2013, 2017; CDPHE-2014, 2017; CDPHE-2015, 2017; IDPH-2014, 2017; IDPH-2015, 2017; SDDOH, 2017; WVDHHR-2014, 2017; WVDHHR-2015, 2017; WVDHHR-2016, 2017). I selected these particular 4 states due to the similarities in the clinically significant CRE characteristics information that was reported to each state health department as well as the population size. Each selected state recently started reporting CRE data as early as 2013 with the latest reports up to 2016. One of the most important factors as to why these 4 states were selected is that all had similar variables reported, which made it a little less problematic when it came to analyzing the independent and dependent variables. Refer to table 4 for the similar CRE characteristics reported from each state that were relevant to this study.

Table 4

CRE Clinically Significant Characteristics Reported Per Selected State

CRE Characteristics	Selected States			
	Colorado	Illinois	West Virginia	South Dakota
Organisms	√	√	√	√
Specimen Sources	√	√	√	√
Facility Types	√	√	√	√
Lab gene Detection Methods	√	√	√	√

The Colorado Department of Public Health and Environment (CDPHE) implemented a regulatory action for laboratories to report CRE information to the state within 7 days of CRE confirmation using the state's electronic disease reporting system effective as of November 30th 2012 (APIC, 2017). Colorado CRE data reported in January thru December of 2013, 2014, and 2015 to the CDPHE were used for the data analysis for this study (CDPHE-2013, 2017; CDPHE-2014, 2017; CDPHE-2015, 2017). The Illinois Department of Public Health (IDPH) implemented a regulatory action that required laboratories and health care facilities to report the first CRE isolate from a patient within 7 days of the finalization of the CRE test result using the state's Extensively Drug-Resistant Organism (XDRO) registry effective as of November 1st 2013 (APIC, 2017). Illinois CRE data reported in January thru December of 2014 and 2015 were used for the data analysis for this study (IDPH-2014, 2017; IDPH-2015, 2017). The West Virginia Bureau for Public Health implemented a protocol requirement

that all laboratories test results that are positive for CRE be reported to the state using the West Virginia Electronic Disease Surveillance System CRE Report Form effective as of August 12th 2013 (APIC, 2017). West Virginia CRE data reported in January thru December of 2014, 2015, and 2016 were used for the data analysis for this study (WVDHHR-2014, 2017; WVDHHR-2015, 2017; WVDHHR-2016, 2017). Lastly, the South Dakota Department of Health updated their list of mandatory reportable disease list to include CRE effective as of July 1st 2013 and any CRE result is to be reported within 3 days of confirmation (APIC, 2017). South Dakota CRE data reported in July thru December of 2013 and January thru December of 2014, 2015, and 2016 were used for the data analysis for this study (SDDOH, 2017).

Data that I used for this study to address the second research question was from the CDC, which included the following 5 different confirmed Carbapenemase gene mechanisms of IMP, VIM, KPC, NDM, and OXA-48 collected from health care facilities in the 4 selected states of Colorado, Illinois, West Virginia, and South Dakota between 2016 to 2017 (CDC, 2017a). The CDC just recently established an Antibiotic Resistance Laboratory Network (AR Lab Network) in 2016 and received additional funding to do confirmatory testing for specific CRE gene mechanisms. The AR lab network mainly tracks changes in antibiotic resistances in order to help identify and respond to outbreaks (CDC, 2017a). The network receives antibiotic resistance information on 50 states, 5 cities, and Puerto Rico through 7 regional laboratories. The 7 regional labs are located in Maryland, Minnesota, New York, Tennessee, Texas, Washington, and Wisconsin. The AR lab network chain of process involves the local health care facility lab sending a

confirmed CRE case sample to the respective public health department lab then the public health department lab will send the CRE case sample to the regional lab, which will be tested again to confirm the CRE gene mechanism and finally the information is sent to the CDC to compile (CDC, 2017a).

The CDC started collecting CRE gene mechanisms data in 2016, and CRE gene mechanism data are available from 2016 to 2017. Currently, the CDC only compiles 5 of the many different types of CRE gene mechanisms that exist, which are IMP, VIM, KPC, NDM, and OXA-48 (CDC, 2017a). The AR lab network is a reliable tool for tracking specific CRE gene mechanisms in health care facilities, but recently CRE cases are emerging outside of health care facilities. The CDC confirmed CRE cases are only part of the crucial CRE picture with community-associated CRE cases being missed, which may result in additional CRE gene mechanism types being undetected.

Population

The limited demographic information available on the 4 selected states' population considered for the first research question is located below in Table 5. In Table 5 information includes the total number of CRE cases collected between 2013 to 2016, sorted by state, gender, and median patient age that were reported with a CRE infection. This information provided an overall view of how patients were affected with CRE. Also available on the 4 selected states were the reported regions for CRE and population size, which can be found below in table 6. The public health regions are the actual regions in which CRE cases were reported as well as the latest population census and the most recent estimated census information. Table 6 also provided a view of the total number of

individuals that could potentially be at exposed risk to community-associated CRE infections if health professionals are not educated and/or informed on CRE.

Table 5

Select States' Individual Available Demographics

Selected States CRE Patient Demographic Information 2013 to 2016				
Characteristics	States			
	Colorado	Illinois	West Virginia	South Dakota
Patient's Median Age	67	65	68	69
Sex				
Female	300	1158	300	75
Male	238	1110	149	70
Patient Totals	538	2268	449	145

Table 6

Selected States CRE Reported Regions and Population Size

State	Public Health Regions	2010 Census Population	2017 Estimated Population
Colorado	Denver, Metropolitan Northeast, Southeast, & Western Slope	5,029,196	5,607,145
Illinois	City of Chicago, West Chicago, Rockford, Peoria, Champaign, Edwardsville, Marion, & Unknown	12,830,632	12,802,023
West Virginia	Southern, Central, Eastern, Western, Northwestern, Northeastern	1,852,994	1,815,857
South Dakota	Pennington, Oglala Lakota, Corson, Ziebach, Dewey, Walworth, McPherson, Edmunds, Faulk, Brown, Spink, Beadle, Clark, Codington, Hamlin, Roberts, Grant, Brookings, Tripp, Brule, Charles Mix, Davison, Minnehaha, Turner, Lincoln, Yankton, Clay, Union	814,180	869,666

As mentioned previously the information on the data selected to address the second research question was compiled gene mechanism confirmed CRE cases from patients with health care acquired CRE cases from the 4 selected states.

Sample and Sampling Procedure

The sampling strategy of nonprobability purposive was the most appropriate for this study due to the exploratory research when trying to determine if an issue exists when limited amount of research currently exists. The sample population selected focuses on the characteristics of interest which are both health care acquired and community-associated CRE cases (Frankfort-Nachmias & Nachmias, 2007). The inclusion criteria

were specific distinct individual categorized clinically significant CRE characteristics reported to a particular state's department of health that was used for comparison as listed above in table 4. The exclusion criteria included no distinct individual clinically significant CRE characteristic of medical facility type reported to the state's department of health and/or state not reporting CRE results at any capacity. The CDC compiled list of confirmed CRE gene mechanisms for the second research question was not an exhaustive population list because currently only health care facilities are reporting their confirmed CRE cases to the CDC and no other types of facilities, which was also under the sampling strategy of non-probability. All of the CDC collected confirmed CRE gene mechanisms of IMP, VIM, KPC, NDM, and OXA-48 compiled data was an inclusion factor with no exclusion factors in order to explore an association of this newly collected data.

Based on a retrospective design type analysis to address both research questions G*Power software was used to determine the sample size, effect size, and power (Bruin, 2006). The statistical test of choice for both research questions was the Goodman and Kruskal's lambda measurement of association analysis after each research question and measurement of variables passed the 2 required assumptions (Laerd, 2016). The first assumption requirement for Goodman and Kruskal's lambda states there should be 1 dependent variable and 1 independent variable. Both dependent and independent variables were on a nominal scale and each variable contained multiple categories such as gender has 2 categories or profession can have 5 categories. An ordinal scale variable could be used with the Goodman and Kruskal's lambda test, but the ordinal status will

not remain after the test has been implemented; therefore, it is recommended to select an alternative test such as Goodman and Kruskal's gamma if an ordinal nature is needed throughout testing (Laerd, 2016). The second assumption requirement for Goodman and Kruskal's lambda states that there should be no relationship between observations within the groups or between the groups which would constitute independence of observations (Laerd, 2016)

For the first research question implementing a measure of association between categorical variables using Goodman and Kruskal's lambda was the most appropriate analysis having an alpha level of 0.05, an effect size of 0.3, power of 0.95, and a noncentrality parameter λ of 19.80 would require a sample size of at least 220. For the second research question also implementing Goodman and Kruskal's lambda also was the most appropriate analysis and it would have the same of an alpha level of 0.05, an effect size of 0.3, power of 0.95, and a noncentrality parameter λ of 19.80 would require a sample size of at least 220 (Bruin, 2006). For this study there were no other studies in the literature review that revealed effect sizes or power predetermined or determined in past studies. This was definitely the first study of its kind and the logic behind the effect size and alpha calculated using G*Power was strictly to get the appropriate samples size to yield at least a power of 0.95

Data Collection

This retrospective study used secondary archival CRE epidemiology summary data from 4 individual state departments of health from Colorado, Illinois, West Virginia, and South Dakota. Access to each state's secondary data sets were available on each

respective website located in their epidemiological summary reports. The Colorado Department of public Health and Environment decided that a population-based surveillance was needed in order to capture the incidence of carbapenem resistance from residents with certain CRE bacterial infection cases over time from 5 different counties for an overall evaluation and this collection of data started in November 2013 to December 2015. The patient data originally collected for the surveillance report included sex, age, organisms, specimen source, facility type, antibiotic susceptibility testing, and PCR testing for Carbapenemase (CDPHE, 2018).

The Illinois Department of Public Health realized that CRE were appearing on their extensively drug-resistant organisms (XDRO's) registry, so of the culture acquisition dated from November 1, 2013 to December 31, 2015 retrieved representing eight different regions in order to evaluate these CRE infections with little to no treatment options. The original data collected for the surveillance report included sex, age, organism, culture type, facility type, lab detection method, and mechanism of resistance (IDPH-2014, 2017; IDPH-2015, 2017).

The West Virginia Department of Health & Human Resources recognized that CRE was developing as community-associated in addition to health care-associated cases and decided in 2013 to make it a requirement to report all confirmed CRE cases. The surveillance reports however only contained data collected from 2014 to 2016 from 6 regional areas. The original data collected included sex, age, race, culture type, organism, specimen source, facility type, and mechanism of resistance (WVDHHR-2014, 2017; WVDHHR-2015, 2017; WVDHHR-2016, 2017).

The South Dakota Department of Health recognized an outbreak of CRE in the northeast region of their state, which put their state on high alert in 2013 to implement a policy to CRE to the reportable disease list. The current surveillance report included data reported from 2013 to 2016. The original data collected from multiple regions include sex, age, race, patient CRE history, specimen source, organisms, mechanism of resistance, facility type, lab detection method, and Carbapenemase producers (SDDOH), 2017).

This retrospective study used secondary archival data of confirmed health care acquired CRE gene mechanisms collected by the CDC from 2016 to 2017 for the 4 selected states of Colorado, Illinois, West Virginia, and South Dakota. Details on the selected clinically significant characteristic CRE variables and the CDC confirmed gene mechanisms that were of value for the data analysis from the selected populations to answer both research questions are listed in table 7 below.

Table 7

Characteristics from the Original Data Collection

Variable Type	Variable Name	Data Source	Measurement
Independent	Geographical Location	Demographics	Nominal
Dependent	Organism	Clinical	Nominal
Dependent	Specimen Source	Clinical	Nominal
Dependent	Facility Type	Clinical	Nominal
Dependent	Lab Detection Method	Clinical	Nominal
Dependent	Carbapenemase Gene Mechanisms	Clinical	Nominal

Table 8

Data details

Data Implementation Details		
Variable Type	Variable Name	Code Naming List
Independent (RQ1 & RQ2)	Four Selected States	Colorado, Illinois, West Virginia, & South Dakota
Dependent-1 (RQ1)	Organism IDs	*E. coli, K. pneumoniae, K. oxytoca, E. aerogenes, E. cloacae, & Enterobacter species*
Dependent-2 (RQ1)	Specimen Source	Urine, Blood, Wound, Rectal, Respiratory, & Intra-abdominal
Dependent-3 (RQ1)	Medical Facility Type	Acute Care, LTACH, LTCF, & Outpatient
Dependent-4 (RQ1)	Lab Gene Detection Method	Molecular Testing, Phenotypic Testing, Antibiotic Susceptibility Testing
Dependent-5 (RQ2)	Confirmed CRE Gene Mechanisms	IMP, VIM, KPC, NDM, & OXA-48

Dependent and Independent Variables

The independent variable group to address both research questions was the 4 selected geographical location consisting of Colorado, Illinois, West Virginia, and South Dakota. The dependent variable set for Research Question 1 was the clinically significant CRE characteristic group consisting of organism IDs, specimen sources, medical facility types, and lab gene detection methods, see Table 8 above for details (long-term acute care hospital – LTACH & long-term care facility – LTCF). For Research Question 2 the dependent variable set was the 5 types of confirmed health care acquired Carbapenemase

mechanisms compiled by the CDC that will include IMP, VIM, KPC, NDM, and OXA-48, see Table 8 above for details.

Data Analyses Plan

SPSS was the statistical software used to perform the analyses for both Research Question 1 and Research Question 2. Since both research questions and variable measurements passed both stated assumptions the Goodman and Kruskal's lambda was be the most appropriate statistical analysis to answer both research questions (Laerd, 2016). It helped determined whether or not there was associations between the nominal variables that were statistically significant while distinguishing between the independent variable and the dependent variable. An asymmetrical statistic such as lambda measured the strength of association and also the proportional reduction in predictive error (PRE) (Laerd, 2016). The original coding of the data was retained for this study. The initial step to preparing the data required extraction from the surveillance reports and importation into an excel file. The cleaning process included but was not limited to editing the data in order to address missing data, deletion of data, and possible outliers just to name a few probable errors that were encountered. A descriptive analysis in the form of frequencies was generated for all variables to ensure the number of records were accurate prior to analysis.

RQ1: What is the association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016?

Statistical analysis: The Goodman and Kruskal's lambda model was used to test the null hypothesis for Research Question 1. The independent variable set were the states divided into 1 group of the 4 selected states and the dependent variable set were the clinically significant CRE characteristics divided into 1 group of the 4 selected characteristics. Results from the analyses were interpreted based on the crosstabulation contingency table, the directional measures table, the proportional reduction error (PRE) value, and the p-value.

RQ2: What is the association between the five types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

Statistical analysis: The Goodman and Kruskal's lambda model was used to test the null hypothesis for Research Question 2. The independent variable set were the states divided into 1 group of the 4 selected states and the dependent variable set were the confirmed Carbapenemase gene mechanism divided into 1 group of the 5 gene mechanisms. Results from analyses were interpreted based on the crosstabulation contingency table, the direction measures table, the proportional reduction error (PRE) value, and the p-value.

Threats to Validity

Using a retrospective study design with secondary data I selected had inherent threats that exist to the internal and external validity. Since the researcher using secondary data do not have control over how the study population, data collection processes, or the quality of data that was originally collected, the lack of random

selection was a potential threat to the internal validity (Creswell, 2009). Conducting a retrospective study with nonprobability sampling was effective in creating a picture of a situation as in the case of this study of creating a possible prevalence picture of community-associated CRE cases in the United States. However, this type of sampling study did have an effect on the generalizability of the end results to the entire population by possibly having a very high confidence level. Nonprobability sampling is good for a hypothesis that has been generated that involves exploratory research, but the results can be biased along with analytical inferences. In addition to only having data that is grouped like the dependent data for this study into categories versus having access to the reported raw data also had an external threat on the representativeness along with the limited scope of the study, but this study is the starting point of future studies with more detailed CRE data that could have the potential to be properly manipulated (Frankfort-Nachmias & Nachmias, 2007)

Ethical Procedures

Institutional Review Board (IRB) approval was granted for this retrospective study using archival data for secondary data usage prior to performing any data analysis. Since the data is archival data Walden University had a shorter more abbreviated IRB application form that was used to get IRB approval. The archival data from all 4 selected state public health departments have been previously published in surveillance reports and the data is de-identified. The public health departments adhere to general data protection regulations (GDPR) and there were no ethical concerns on the patient collected data. The data selected from the CDC was also published data on the CDC website that

has also been de-identified and the CDC also adheres to GDPR on all collected data. The data integrity and confidentiality employed concerning this study will be maintaining the data collected for at least 5 years after study completion. To ensure secure data storage during the 5-year date duration all study data is stored in a password protected folder on a password protected computer.

Summary

In summary, the research methodology used to explore the prevalence of community-associated and health care acquired CRE cases with similar clinically significant characteristics that were in the form of a quantitative nonexperimental retrospective study using nonprobability sampling secondary data from the public health departments from 4 selected states and confirmed Carbapenemase gene mechanisms from the same 4 selected states and compiled by the CDC from the AR lab network. Two research questions were formulated to help determine the measure of the strength associated between clinically significant CRE reported characteristic and confirmed CRE gene mechanisms for 4 selected states. The secondary data sets were accessed from previously published surveillance reports and established CDC website reports.

The data analyses plan included using the statistical software program SPSS in order to perform a Goodman and Kruskal's lambda analyses for both research questions. A power of analysis was conducted for each individual research question that determined the appropriate sample size, alpha level, and effect size. Detailed information on the population demographics and the original CRE characteristics data were provided.

Details were also provided on the dependent and independent variables. Lastly the threat to internal and external validity and ethical procedures were addressed.

Chapter 4: Results

Introduction

My purpose for this quantitative nonexperimental retrospective study was to explore the prevalence association of CRE cases that have been reported between the years of 2013 thru 2016 as community-associated CRE cases and as health care acquired cases associated with the similar reported clinically significant CRE characteristics of organism identifications (*E. coli, K. pneumoniae, K. oxytoca, E. aerogenes, E. cloacae, & Enterobacter species*); specimen sources (urine, blood, wound, rectal, respiratory, & intra-abdominal); medical facility types (acute care, long-term acute care hospital – LTACH, long-term care facility – LTCF, & outpatient); and laboratory CRE gene mechanism detection methods (molecular testing, phenotypic testing, & antibiotic susceptibility testing) that had been reported to the respective state health departments in Colorado, Illinois, West Virginia, and South Dakota. For this study I also explored the association of 5 confirmed Carbapenemase gene mechanisms of Imipenemase (IMP), Verona Integron-encoded Metallo-beta-lactamase (VIM), Klebsiella pneumoniae Carbapenemase (KPC), New Delhi Metallo-beta-lactamase (NDM), and Oxacillinase-48 (OXA-48) from the same 4 states of Colorado, Illinois, West Virginia, and South Dakota complied by the CDC as of 2017 from their Antimicrobial Resistant (AR) Laboratory Network to analyze the association of the confirmed Carbapenemase gene mechanism cases between the 4 states.

The scope limitations I stated for this study were as follows: the data were only available in groups reported in respective state surveillance reports, since the groups were

not randomly selected or assigned manipulation of the independent and dependent variables were not possible. The CRE data reported to the respective state public health departments during 2013 thru 2016 were the very first of that type of data reported. The CRE confirmed gene mechanism data from the CDC as of 2017 was also the first of that type of information reported. The research questions and hypotheses of this study were as follows:

Research Question 1: What is the association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016?

$H_0$1: There is no association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

$H_1$1: There is an association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

Research Question 2: What is the association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

$H_0$2: There is no association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

$H_1$2: There is an association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

Chapter 4 presents information related to the data collection processes and the results achieved from the analyses. I performed a compilation of the descriptive analyses for independent and dependent variables. The findings were presented for each research question and variable. There is a summary of the primary findings of the study conducted, and finally a transition into the interpretation of these findings in chapter 5.

Data Collection

The secondary data I collected for this study were obtained from 2013 thru 2017 collectively from the respective state health departments of Colorado, Illinois, West Virginia, and South Dakota and confirmed gene mechanisms from the CDC as of 2017. The secondary archival CRE epidemiology summary data reports from the state health departments of Colorado, Illinois, West Virginia, and South Dakota I accessed through each respective state health department website and the CDC data were accessed through the CDC website.

There was a small discrepancy in the data collection plan originally presented in chapter 3. The 5 confirmed gene mechanisms data of IMP, VIM, KPC, NDM, and OXA-48 collected by the CDC were available according to the website for the exception of the KPC gene mechanism. There were no actual total number of cases reported on the CDC website for the KPC gene mechanism; it only listed if each state had reported KPC cases. I contacted the CDC in April 2019 to asked about how to get the actual number of KPC

cases. After several weeks and corresponding originally by phone then by email with several CDC representatives, I finally received an answer that the CDC historically have not tracked the KPC CRE counts like the other 4 carbapenemase gene mechanisms because the frequency of KPC CRE is so much greater. The CDC suggested that I reach out to the respective state's health department personnel to get actual KPC CRE counts. I reached out to each state's health department to get their respective KPC CRE counts. It took an additional 2 weeks to obtain the KPC counts, but I was able to get total KPC counts for the years that each state started collecting CRE epidemiology information.

Sample Demographic Characteristics

The secondary data for this study I extracted from the archival CRE epidemiology summary reports from 4 individual state departments of health from Colorado, Illinois, West Virginia, and South Dakota available on each respective state's website. Secondary data I also extracted from the CDC website for the confirmed health care acquired CRE gene mechanism for the exception of the KPC confirmed gene mechanism, which came from each of the 4 states selected.

I complied all of these data into total category sets by independent variable group of each of the 4 states and by each dependent variable group of gene mechanism, organism ID, specimen source, facility type, and lab detection method; see Table 9 below for sample characteristics details. By performing the Goodman and Kruskal lambda statistical test I was able to run the analyses using total counts (frequencies) rather than individual scores, so I opted for that function which required the cases to be weighted using SPSS processes prior to executing the actual Goodman and Kruskal lambda

analysis (Laerd Statistics, 2016). The case weight process I executed by performing the 'weight case by' function in SPSS, which involved using each clinical characteristic variable group and each frequency total for that particular characteristic group (Laerd Statistics, 2016). There were no missing data after all of the data was compiled from the epidemiology reports. There were instances where there were no data collected which was recorded as 0 for the analysis then listed as N/R in each respective table, so no data were considered missing. The representative sample population cases generated from the 4 states were in the thousands and can be seen as proportional to a larger population for generalizability of the results.

Table 9

CRE Case Summaries

	CRE Case Summaries					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Gene Mechanism	1039	100.0%	0	0.0%	1039	100.0%
Type of Organism ID	4021	100.0%	0	0.0%	4021	100.0%
Type of Specimen Source	3950	100.0%	0	0.0%	3950	100.0%
Medical Facility Type	4243	100.0%	0	0.0%	4243	100.0%
Lab Detection Method	4482	100.0%	0	0.0%	4482	100.0%

Analysis Results

For Research Question 1, four detailed analyses were completed using Goodman and Kruskal's lambda statistical test for the dependent variables' organism ID, specimen source, medical facility type, and lab gene detection method and for the independent variable, state. See the descriptive statistics for each analysis in Tables 10, 11, 12, and 13. An evaluation of the hypotheses follows each result analysis.

Research Question 1: What is the association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016?

$H_0$1: There is no association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

$H_1$1: There is an association between CRE organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method and geographical location (Colorado, Illinois, West Virginia, and South Dakota) from 2013 to 2016.

Table 10

Organism ID Descriptive Statistics

State	Organism Identification (ID)					Total
	E. coli	*K. pneumoniae*	*E. aerogenes*	*E. cloacae*	*Enterobacter species*	
Colorado	67	46	72	336	5	526
Illinois	180	2567	N/R	N/R	170	2917
West Virginia	46	153	77	159	11	446
South Dakota	9	67	9	46	1	132
Total	302	2833	158	541	187	4021

Note. N/R = none reported.

I used Goodman and Kruskal's λ to determine whether the CRE organism ID isolated and reported by the state's health department could be better predicted by knowledge of the state where the CRE organism ID originated from. The Goodman and Kruskal's λ was .249. This was a statistically significant reduction in the proportion of errors due to knowledge of the selected state as a predictor of CRE organism ID isolated, $p<.001$. The alternate hypothesis that there is a significant association for the organism ID between the 4 states is supported which rejects the null hypothesis that there is no association. The organism ID most abundantly reported was K. pneumoniae and from Illinois; in addition, the state of Illinois did not report any E. aerogenes or E. cloacae organism IDs. The remaining states all had data reports for all 5 organism IDs.

Table 11

Specimen Source Descriptive Statistics

State	Specimen Source Type						Total
	Urine	Blood	Wound	Rectal	Respiratory	Intra-abdominal	
Colorado	341	39	31	34	37	37	519
Illinois	1469	N/R	356	556	396	N/R	2777
West Virginia	375	15	53	16	51	N/R	510
South Dakota	83	1	19	19	19	3	144
Total	2268	55	459	625	503	40	3950

Note. N/R = none reported.

I used Goodman and Kruskal's λ to determine whether the CRE specimen source type reported to the state's health department could be a better predicted by knowledge of the state where the CRE specimen source type originated from. The Goodman and Kruskal's λ was .000. This is not a statistically significant reduction in the proportion of errors due to knowledge of the state as a predictor of the specimen source type reported. The alternative hypothesis that there is a significant association for specimen source between the 4 states is not supported. The null hypothesis cannot be rejected. The specimen source most abundantly reported was urine followed by rectal, respiratory, and wound. Blood and intra-abdominal represented the least reported specimen sources by the states. Illinois did not have any reported data for either blood or intra-abdominal

specimen sources. West Virginia did not have any reported data for the intra-abdominal source.

Table 12

Medical Facility Type Descriptive Statistics

State	Medical Facility Type				Total
	Acute Care	LTACH	LTCF	Outpatient	
Colorado	339	22	56	121	538
Illinois	1817	658	N/R	802	3277
West Virginia	154	N/R	130	N/R	284
South Dakota	82	N/R	29	33	144
Total	2392	680	215	956	4243

Note. N/R = none reported. LTACH = Long-Term Acute Care Hospital. LTCF = Long-Term Care Facility.

I used Goodman and Kruskal's λ to determine whether the type of medical facility reported to the state's health department could be better predicted by knowledge of the selected state where the medical facility is located. The Goodman and Kruskal's λ was .000. This was not a statistically significant reduction in the proportion of errors due to knowledge of the selected state as a predictor of type of medical facility. The alternative hypothesis that there is a significant association for medical facility type between the 4 states is not supported. The null hypothesis cannot be rejected. Acute care was the leader for most reported data followed by outpatient then long-term acute care hospital finally long-term care facility with the least reported. Illinois did not have any reported long-term care facility data, but remained the leader in the most reported of all

facilities combined. South Dakota had no reported long-term acute care hospital data along with west Virginia. West Virginia did not have any reported outpatient data, which will be discussed more at length in chapter 5.

Table 13

Lab Gene Detection Method Descriptive Statistics

State	Lab Gene Detection Method			Total
	Molecular Testing	Phenotypic Testing	Antibiotic Susceptibility Testing	
Colorado	282	N/R	352	634
Illinois	709	1574	882	3165
West Virginia	N/R	N/R	490	490
South Dakota	55	55	83	193
Total	1046	1629	1807	4482

Note. N/R = none reported.

I used Goodman and Kruskal's λ to determine whether the type of lab gene detection method reported to the state's health department could be better predicted by knowledge of a particular state where the lab gene detection method was performed. The Goodman and Kruskal's λ was .259. This was a statistically significant reduction in the proportion of errors due to knowledge of a particular state as a predictor of the type of lab detection method, $p<.001$. The alternate hypothesis that there is a significant association for the lab detection method between the 4 states is supported which rejects the null hypothesis that there is no association. The leader for lab gene detection method among

the 4 states was antibiotic susceptibility testing followed by phenotypic testing with molecular testing with the least at 1046 reported using that detection method. The state of Colorado had no reported phenotypic testing data along with West Virginia. West Virginia was the only state with no reported molecular testing performed.

For Research Question 2 a detailed analysis was completed using Goodman and Kruskal's lambda statistical test for the dependent variable group of confirmed health care acquired Carbapenemase gene mechanisms for the independent variable group of 4 states. See the descriptive statistics for analysis in Table 14. An evaluation of the hypothesis follows the result analysis.

Research Question 2: What is the association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017?

$H_0$2: There is no association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

$H_1$2: There is an association between the 5 types of confirmed health care acquired Carbapenemase gene mechanisms and geographical location (Colorado, Illinois, West Virginia, and South Dakota) reported to the CDC as of 2017.

Table 14

Gene Mechanisms Descriptive Statistics

State	Gene Mechanisms					Total
	IMP	VIM	KPC	NDM	OXA-48	
Colorado	N/R	1	31	25	N/R	57
Illinois	3	1	636	109	13	762
West Virginia	N/R	N/R	153	N/R	N/R	153
South Dakota	N/R	N/R	67	N/R	N/R	67
Total	3	2	887	134	13	1039

Note. N/R = none reported.

I used Goodman and Kruskal's λ to determine whether the type of gene mechanism reported to the CDC or by the state's health department could be better predicted by knowledge of a particular state where the gene mechanism was isolated. The Goodman and Kruskal's λ was .000. This was not a statistically significant reduction in the proportion of errors due to knowledge of a particular state as a predictor of type of gene mechanism isolated. The alternative hypothesis that there is a significant association for carbapenemase gene mechanism between the 4 states is not supported. The null hypothesis cannot be rejected. The only state that had all 5 confirmed health care acquired gene mechanism reported to the CDC was Illinois followed by Colorado with 3 of the 5 confirmed gene mechanisms reported to the CDC. West Virginia and South Dakota only reported the one KPC confirmed health care acquired gene mechanism to the CDC. The total number of health care acquired confirmed gene mechanism among the 4 states combined is far less than the total activity of the clinical characteristics listed for

both health care acquired and community-associated CRE reports for the analyses completed for Research Question 2.

Summary

The analyses of the secondary data I performed for this study tested the hypotheses of the 2 research questions. Research Question 1 (RQ1) contained the dependent variable of a clinical characteristics group that encompassed 4 characteristics (CRE organism ID, specimen source, medical facility type, and lab gene mechanism detection method) between the independent variable group that encompassed 4 selected states (Colorado, Illinois, West Virginia, and South Dakota). The results I generated from the analysis performed between the organism ID and the selected 4 states with a λ of .249, $p<.001$ and the results between the lab detection method and the selected 4 states with a λ of .259, $p<.001$ produced a significant association result of which the alternative hypothesis was supported for each of those particular characteristics. The results I generated from the analyses performed between the specimen source and the selected 4 states with a λ of .000 and the results between the medical facility type and the selected 4 states with a λ of .000 of which no significant association exists and fails to reject the null hypothesis.

Research Question 2 (RQ2) contained the dependent variable group that encompassed 5 confirmed gene mechanisms (IMP, VIM, KPC, NDM, and OXA-48) between the independent variable group that encompassed 4 selected states (Colorado, Illinois, West Virginia, and South Dakota). The results I generated from the analysis performed between the confirmed gene mechanisms and the 4 selected states with a λ of

.000 of which no significant association exists and fails to reject the null hypothesis. The representative sample population was abundant subsequently making generalization very possible. Chapter 5 includes the interpretation of the result findings, limitations of the study, recommendations for further research, and social change implications.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

For this study I used a quantitative nonexperimental design that used retrospective secondary data analysis using community-associated and health care acquired CRE cases reported between 2013 thru 2016 which was compiled from 4 selected state public health departments from Colorado, Illinois, West Virginia, and South Dakota as the independent variable group. The first dependent variable group comprised of reported clinically significant CRE characteristics of organism ID, specimen source, medical facility type, and laboratory gene mechanism detection method. The second dependent variable group comprised of 5 confirmed health care acquired Carbapenemase gene mechanisms of IMP, VIM, KPC, NDM, and OXA-48 from the CDC. All data details have been previously outlined. The actually KPC numbers were obtained from each state department of health. The reason I conducted this study was to explore the prevalence of the CRE infection cases, both community-associated and health care acquired, to determine if an association exists between geographic location and clinically significant CRE characteristics.

Knowing the state where the CRE infection was reported reduced the probability of making an incorrect prediction on the organism ID by 24.9%, which makes it an association relationship between the selected states of (Colorado, Illinois, West Virginia, & South Dakota) and the organism ID of (*E. coli, K. pneumoniae, E. aerogenes, E. cloacae, Enterobacter species*). Knowing the reporting state also reduced the probability of making an incorrect prediction on the lab detection method by 25.9%, which makes it an association relationship between the selected states of (Colorado, Illinois, West

Virginia, & South Dakota) and the lab gene detection method of (Molecular testing, Phenotypic testing, & Antibiotic susceptibility testing).

Between the selected states of (Colorado, Illinois, West Virginia, & South Dakota) and specimen sources (Urine, Blood, Wound, Rectal, Respiratory, & Intra-abdominal), medical facility types (Acute care, LTACH, LTCF, & Outpatient), and the 5 health care confirmed Carbapenemase genes (IMP, VIM, KPC, NDM, & OXA-48) all produced lambda values of 0 making it a no association relationship between those independent and dependent variable groups.

Interpretations of the Findings

This study extends the knowledge of the very small list of existing studies exploring community-associated CRE factors in the United States. Results highlighted that knowing the organism ID and/or lab detection method from the 4 different selected states can reduce the probability of making an incorrect prediction for community-associated CRE infections. Results also highlighted that there was a no association relationship for the specimen source, medical facility type, and the 5 confirmed carbapenemase gene mechanism between the 4 different selected states. Additional collaborative detailed data are needed on the characteristics of specimen source, medical facility type, and the 5 confirmed carbapenemase gene mechanism from community-associated sources as well as continued health care acquired sources in order to further the knowledge.

Since the data collected by the 4 selected states was the first time any data of this type had been collected on community-associated and health care acquired CRE, it would

be significant to this study to discuss the detailed results in more depth beyond just the lambda result values. Looking back at the organism ID descriptive statistics listed in Table 10, *K. pneumoniae* was the most abundant organism ID collected for CRE for both health care acquired and community-associated CRE with 2833 total reported by all 4 selected states, but the total number of KPC health care acquired gene mechanism reported to the CDC was only 887 (Table 14). The fact remains that a total of 1946 cases of KPC CRE cases from the 4 selected states were not being considered by the CDC total count reports. The 887 CRE health care acquired cases reported to the CDC represented only a little more than 31% of the actual KPC cases that existed overall during the years of 2013 thru 2017 for the 4 states combined. This is significant in the fact that the complete KPC picture from 2013 to 2017 was not fully considered by the entire health care arena albeit health care acquired or community-associated. This could be a significant factor that could have contributed and can continue to contribute to the rise of community-associated CRE in the United States. Literature revealed that since the resistance classification named Klebsiella pneumoniae carbapenemase (KPC) came into existence it has rapidly and steadily increase, which is still a fact (Guh et al., 2014). Upon further exploration of the results detailed in Table 10 revealed that as of 2016 Illinois did not have any reported CRE organism IDs of *E. aerogenes* or *E. cloacae* which could be significant baseline exposure information if Illinois reports any of those two organism IDs in the future.

For specimen source (Table 11), urine dominated the totals with 2268 cases compared to the other 5 specimen sources reported which was a significant number of

positive CRE cases that involved the source of urine. Results from a past global study revealed that there was evidence of an initial diagnosis of a positive CRE culture could have a mean time of 387 days to proven CRE negative (Zimmerman et al., 2013). This could be an important fact to consider when those 2268 CRE urine cases time frame it took for the patient to be treated from a positive CRE urine culture state to a negative CRE urine culture state, so again possible factors contributing to the rise of community-associated CRE in the United States. due to the many urinary tract infections that are commonly treated in outpatient clinics.

I examined the medical facility type descriptive statistics further listed in Table 12 and it revealed that the most abundant medical facility type reported was acute care facility, but it was discovered that there were deficiencies in the definition of the medical facility types for the LTACH, LTCF, and outpatient when compared between states meaning not each state had the same exact definition for each facility type. Since this was the first time the selected states reported different medical facility types in the future it would be helpful to have a more universal definition for each medical facility type to help states report more precisely, which will help with a more precise and accurate comparison. West Virginia was selected and very significant to this study with regards to the outpatient medical facility type description category. West Virginia clearly noted in the 2016 surveillance report that while some CRE infections may be acquired in the community they do not track resistance mechanisms from laboratories due to CRE being historically associated with exposure to health care facilities which is why West Virginia had no reported outpatient cases (WVDHHR-2016, 2017). After I explored the data

details in all of the tables for West Virginia and considering they acknowledged that community-associated CRE exists but they do not track the resistance mechanisms from outpatient laboratories is very alarming because West Virginia could potentially have under reported major CRE results (WVDHHR-2016, 2017) . Since West Virginia had significant numbers of organism IDs, specimen sources with reported CRE information from only 2 medical facility types, reported only antibiotic susceptibility, and reported only KPC gene mechanisms from that state, West Virginia could expressively be contributing to those factors significant in the rise of community-associated CRE in the United States.

I examined the lab gene detection methods, which revealed that Illinois, the largest state reporting, was able to report the most results using the molecular methods than the other listed detection methods. Antibiotic susceptibility testing is considered the least expensive followed by phenotypic testing and then molecular testing methods (Hrabák et al., 2014). Molecular testing methods are the most accurate and precise methods for confirmation of different gene resistance mechanisms that exist in the health care field (Hrabák et al., 2014). Depending on a facility's budget and the experience of the health care professional would determine which detection method is used the most frequent (Hrabák et al., 2014).

Exactly how CRE infections have emerged into the community-associated category in the United States is still evolving. A close examination of the study results made it clear that more detailed data are needed to be collected and analyzed on a more consistent basis from more states. Identification of CRE gene mechanisms is a very

important step to the identification of which patients are infected with what mechanism, in order to properly apply surveillance to keep transmission of these gene mechanism transfer low (Kaye & Pogue, 2015; Rolain & Cornaglia, 2014). Having a tool of lab gene detection method can continue to help with identification of the gene mechanism which this study confirmed has a significant association relationship of prediction. Hopefully, with this study I will provide the catalyst needed for more in-depth future studies with more detailed clinical characteristics involving community-associated CRE infections that can be connected in order to provide even more great insight to the emerged community-associated CRE in the United States.

The theoretical framework of One Health embodies a collaborative approach to reducing health risks such as antibiotic resistance like CRE infections (Solomon, 2017). One Health promotes optimum health through continuous joint efforts of all health professionals, health facilities, scientists, organizations, and disciplines (Solomon, 2017). The One Health theory supports the fact that antibiotics that are used for humans and animals share some of the same molecules, which makes transmission of resistance easier and easier. If all entities join forces in tackling AMR, such as CRE, a reduction in health care and financial burden may improve the public health sector (Solomon, 2017).

The 4 states I selected for this study were specifically targeted for the similar clinical characteristics that were reported involving community-associated and health care acquired CRE infections. The result findings of organism ID and lab gene detection method between the 4 selected states having a significant association relationship helped confirm that the One Health theory of collaborating in the form of reporting similar and

specific clinical characteristics can help strengthen the overall joint efforts on CRE infection surveillance. The Goodman and Kruskal's λ results for the CRE organism and lab gene detection method between the 4 selected states are very close in value (.249 and .259 respectively). At first observation these 2 lambda results could be regarded statistically as predictor variables that are highly correlated causing collinearity meaning they expressed a linear relationship (Laerd, 2016). However, collinearity tends to happen in regression type analyses that use continuous variables that are of an ordinal nature. The Goodman and Kruskal analyses I performed determined the strength of association between categorical variables with 3 or more levels, which makes the collinearity logic nonapplicable for these lambda results (Laerd Statistics, 2016). Each of my variable groups were independent of each other. Moreover, from a laboratory practice observation the CRE organism and lab gene detection method are correlated due to the fact that when both results are known it strengthens the predictability for CRE infections surveillance.

Even though specimen source, medical facility type, and the 5-health care confirmed Carbapenemase gene did not produce an associated relationship in this study it could still be a catalyst for future studies with more detailed data involving specimen source, medical facility type, and the 5 confirmed Carbapenemase genes as well as more defined definitions of characteristics. After examining the data detailed in the result tables there is much more work to be done to fight this battle against community-associated and health care acquired CRE in the United States. Even though the results from this study could not provide the specific and concise understanding of just how CRE infections have evolved from health care acquired sources to now community-associated

sources this study did provide informational possibilities of how community-associated sources could happen.

Limitations of the Study

For this retrospective study I used secondary data as a nonprobability sampling of convenience, but nonrandomized or not being assigned in selected groups of data was one of the inherent limitations of this study. Inherent validity threats both internal and external existed using a retrospective type of study design. This type of study was effective in the creation of a prevalence picture of community-associated CRE cases in the United States. since this scenario is still fairly new.

Another limitation of this study was that each state's data were reported in categorical groups instead of individual specifics, so the results were presented in 5 different clinical characteristic groups for the 4 selected states. It was not possible to manipulate the data as to compare or do an analysis for example between which facility (e.g. acute or outpatient) reported which gene mechanism type (e.g. KPC or VIM). It was also not possible to calculate any trends for any of the data as a comparison. Moreover, the previous mentioned limitation also created a strength for this study which was the large sample data numbers generated after compiling all of the data from the surveillance reports from each of the 4 selected states. So, the high yield number of data collected for the study that involved the clinical characteristics of organism ID, lab detection methods, medical facility types, specimen sources, and gene mechanisms between the selected states generated end results for the generalizability to an entire population was not a problem.

Recommendations

Referencing back to the theoretical foundation framework of One Health I selected for this study, the concept promotes people, animals, and the environment that can achieve optimum health (Solomon, 2017). Continuous joint efforts based on the fact that antibiotics used for human and animals share the same molecules which makes transmission for antibiotic resistance easier than realized between humans and animals either directly or by way of the environment (Solomon, 2017). One Health supports expanding surveillance from just solely focused on human antibiotic and consumption data from hospitals and community to also incorporating surveillance data to included animals, food, and the environment (Queenan et al., 2016). Although addressing animal, food, and the environment for community-associated CRE for data analysis was out of scope for this study, existing literature were reviewed on those sources when exploring CRE gene transmission. The literature I reviewed was quite compelling and introduced several factors that exist in other countries but have not yet been explored in the United States before that suggests other facets of community-associated CRE gene acquired and transmission cases (Abraham et al., 2014; Guerra et al., 2014). One of those compelling studies was conducted in Australia by researchers that involved the relationship between humans and their companion pets by way of cross bacteria species transmission (Abraham et al., 2014). Another compelling study was conducted in Germany by researchers that involved food producing sources such as livestock, wildlife, and seafood and the gram negative organism relationship between soil and irrigation water (Guerra et al., 2014). These studies are just a few examples that could only bring about awareness to

the possibility of other alternative sources of CRE exposures from the community for future studies in the United States.

The end study results and literature review information generated from this study are also definite catalysts for further research for the exploration of other factors contributing to community-associated CRE infection in the United States. In order to fully comprehend the migration of CRE from health care type facilities only is to also include community type setting as well. The biggest recommendation would be for the CDC to get more involved in the surveillance of CRE cases other than just health care acquired due to the exponential rise in community-associated CRE. The individual U.S. states are putting forth an effort but will need guidance in what details to report for across the board consistent clear definitions on clinical characteristics such as facility types and categories (e.g. laboratory, outpatient) for future concise result reporting.

Social Change Implications

With this study I confirmed that having the knowledge of some specific clinical characteristics related to community-associated CRE infections can improve the knowledge of what factors can be used to predict their existence, which is a start that can help improve public CRE health. Even though this study was small in nature it added some new information to the small number of existing studies of CRE contributing factors in the United States. and this is a serious potential social change implication. Any positive information can start to build upon the contribution greatly needed at reducing the spread of CRE infections which can also help in the reduction of the economic burden of CRE infections associated with the per capita cost of health care no matter how

miniscule the knowledge. The number 1 goal is to continue to provide information that will contribute to actions that will preserve the carbapenem class of antibiotics for when they are truly needed while at the same time preserving the quality of life which will also help save lives. Hopefully this study along with the other few studies that exist on contributing factors to community-associated CRE will capture the attention of health professionals, health care facilities prescribers, researchers, state health departments and policymakers to improve practices, policy, and the collection of surveillance data pertaining to antibiotic resistance overall with special attention to CRE infections. This collaboration would be a perfect example of the One Health theoretical processes at work for tackling antibiotic resistance for the future.

Conclusion

With the results of this study I established for the first time a significant association relationship for the clinical characteristics of organism ID and lab gene detection method between the selected states of Colorado, Illinois, West Virginia, and South Dakota. By knowing the selected states, a reduction in the probability of making an incorrect prediction on the organism ID and lab gene detection method is a major breakthrough for added knowledge to factors contributing to community-associated CRE infections in the United States.

My purpose for this study was to explore the prevalence of CRE infection cases that have been reported between 2013 thru 2016 as community-associated CRE cases and as health care acquired cases. The similar reported clinically significant CRE characteristics of organism identification, specimen source, medical facility type,

laboratory CRE gene mechanism detection method, and the 5 confirmed carbapenemase mechanism IMP, VIM, KPC, NDM, and OXA-48 were compared between the 4 selected states of Colorado, Illinois, West Virginia, and South Dakota. In this study I was productive and successful in providing valuable information regarding CRE prevalence.

Although my study's positive associated results achieved were small it provided a big step towards a connection in the predictions of organism ID and lab gene detection methods. Moreover, this study's negative associated results provide some useful information for possible future studies. Unless all health care entities join forces together CRE infections regardless of the origin health care acquired and community-associated will not improve unless some action has been taken. The public's health deserves a future free of CRE prevalence cases regardless if it is health care acquired or community-associated. The public's health deserves to have antimicrobials that will work for difficult to treat infections when needed. The alternative will be CRE cases that will continue to grow along with the health care costs, the financial burden, and no available antimicrobials to treat difficult infections. Just say no to the alternative scenario.

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